2.3. DIAGNOSIS: LABORATORY TESTS

Authors: Noam Shohat, Susan Odum

QUESTION 1: What is an acceptable sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for a diagnostic tool for periprosthetic joint infections (PJIs)?

RECOMMENDATION: The validity of a diagnostic tool is traditionally measured by sensitivity, specificity, PPV and NPV. A perfect diagnostic tool would be able to correctly classify 100% of patients with PJIs as infected and 100% of aseptic patients as non-infected. Without a perfect test available, we are left to balance between sensitivity and specificity; increasing one would reduce the other. To reduce the rates of false positives and negatives it is extremely important to take into account the pretest probability for infection, derived from patient risk factors, clinical examination and any other examinations available at the point of assessment.

Table 1. Variety of diagnostic tools for PJI

Variable	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Serum testing	98.5%* (96.2-99.6)	100% (97.6-100)	100% (100-100)	97.5% (93.7-99.1)
Synovial fluid testing	100%* (98.3-100)	100% (85.2-100)	100% (100-100)	100% (100-100)
Intraoperative Findings	92.9% (80.5-98.5)	95.8% (78.8-99.9)	97.5% (85.1- 99.6)	88.5% (72.0-95.8)
Overall	96.9% (93.8-98.8)	99.5% (97.2-100)	100% (99.7-100)	96.7% (93.3-98.4)

CI, confidence interval
*Sensitivity for being diagnosed as infected or for moving forward for additional workup.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 79%, Disagree: 10%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

The validity of a diagnostic tool is traditionally measured by sensitivity, sensitivity, PPV and NPV. Validity is the accuracy of a test, or, whether a test measures what it is supposed to measure. A perfect diagnostic tool would be able to correctly classify 100% of patients with PJIs as infected and 100% of aseptic patients as non-infected. Without a perfect test available, we are left to balance between sensitivity and specificity; increasing one would reduce the other. To reduce the rates of false positives and negatives, it is extremely important to take into account the pretest probability for infection [1–3], derived from patient's risk factors, clinical exams and any other exams available at the point of assessment.

When approaching a patient with a failed total joint arthroplasty (TJA), PJI should always be kept in mind. At different points and timing of the investigation, we are willing to accept different sensitivities and specificities. In a recent study, a stepwise approach was used to develop an evidence-based algorithm for diagnosing PJIs. This stepwise approach enables us to maximize sensitivity and specificity for each step based on the timing of the encounter, previous tests available and invasiveness (Table 1).

In the first patient encounter, we typically rely on risk factors, clinical findings and simple serum markers to further guide us. At an early stage we want the tests to be a sensitive as possible, as misdiagnosing an infection as aseptic could lead to devastating outcomes. Interestingly, even if serum testing (as a screening tool) is negative, the risk for PJI is 2.5%. This emphasizes the importance of a pretest probability, patients with a high clinical suspicion based on timing from last surgery (< 2 years), number of surgeries on the joint and positive clinical findings such as erythema, tachycardia and reduced range of motion should be further investigated to increase sensitivity in this stage [4–7].

Synovial fluid aspiration is the next step in the investigation. In recent years numerous markers have been shown to be highly sensitive and specific [8–15]. The fact that patients undergoing synovial fluid testing are already identified as having a high risk for PJIs, the addition of the advantages of more knowledge about synovial fluid analysis garnered in recent years, allows the practitioner to have a very good performance test with high sensitivity (100%) and high specificity (100%). A majority of patients will be diagnosed in this stage.

When a definite diagnosis is not made by this point, intraoperative findings should be used to aid in the diagnosis. Patients not diagnosed as infected or aseptic at this point are usually patients with a dry tap or an overt infection in which the diagnosis is difficult. Thus, this stage holds a relatively low sensitivity and specificity and in 15% of the patients reaching this stage, a diagnosis cannot be made. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Pointing out this unique group of patients promotes awareness in both clinical practice and calls for further research and novel technologies to reduce the number of patients in the gray area in an attempt to improve sensitivity and specificity in these borderline patients.

REFERENCES

[1] Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997;350:1795–1798. doi:10.1016/S0140-6736(97)08140-3.

[2] Akobeng AK. Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. Acta Paediatr. 2007;96:487–491. doi:10.1111/j.1651-2227.2006.00179.x.
[3] Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979;300:1350–1358. doi:10.1056/NEJM197906143002402.
[4] Tsaras G, Osmon DR, Mabry T, Lahr B, St Sauveur J, Yawn B, et al. Incidence, secular trends, and outcomes of prosthetic joint infection: a population-based study, olmsted county, Minnesota, 1969-2007. Infect Control Hosp Epidemiol. 2012;33:1207–1212. doi:10.1086/668421.
[5] Peel TN, Cheng AC, Buising KL, Choong PFM. Microbiological aetiology, epidemiology, and clinical profile of prosthetic joint infections: are current antibiotic prophylaxis guidelines effective? Antimicrob Agents Chemother. 2012;56:2386–2391. doi:10.1128/AAC.06246-11.
[6] Duff GP, Lachiewicz PF, Kelley SS. Aspiration of the knee joint before revision arthroplasty. Clin Orthop Relat Res. 1996:132–139.
[7] Sendi P, Banderet F, Graber P, Zimmerli W. Clinical comparison between exogenous and haematogenous periprosthetic joint infections caused by Staphylococcus aureus. Clin Microbiol Infect. 2011;17:1098–1100. doi:10.1111/j.1469-0691.2011.03510.x.
[8] Patel R, Alijanipour P, Parvizi J. Advancements in diagnosing periprosthetic joint infections after total hip and knee arthroplasty. Open Orthop J. 2016;10:654–661. doi:10.2174/1874325001610010654.
[9] Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Diagnosing periprosthetic joint infection: has the era of the biomarker arrived? Clin Orthop Relat Res. 2014;472:3254–3262. doi:10.1007/s11999-014-3543-8.
[10] Lee YS, Koo KH, Kim HJ, Tian S, Kim TY, Maltenfort MG, et al. Synovial fluid biomarkers for the diagnosis of periprosthetic joint infection: a systematic review and meta-analysis. J Bone Joint Surg Am. 2017;99:2077–2084. doi:10.2106/JBJS.17.00123.
[11] Tischler EH, Cavanaugh PK, Parvizi J. Leukocyte esterase strip test: matched for musculoskeletal infection society criteria. J Bone Joint Surg Am. 2014;96:1917–1920. doi:10.2106/JBJS.M.01591.
[12] Wyatt MC, Beswick AD, Kunutsor SK, Wilson MJ, Whitehouse MR, Blom AW. The alpha-defensin immunoassay and leukocyte esterase colorimetric strip test for the diagnosis of periprosthetic infection: a systematic review and meta-analysis. J Bone Joint Surg Am. 2016;98:992–1000. doi:10.2106/JBJS.15.01142.
[13] Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Combined measurement of synovial fluid α-Defensin and C-reactive protein levels: highly accurate for diagnosing periprosthetic joint infection. J Bone Joint Surg Am. 2014;96:1439–1445. doi:10.2106/JBJS.M.01316.
[14] Omar M, Ettinger M, Reichling M, Petri M, Guenther D, Gehrke T, et al. Synovial C-reactive protein as a marker for chronic periprosthetic infection in total hip arthroplasty. Bone Joint J. 2015;97-B:173–176. doi:10.1302/0301-620X.97B2.34550.
[15] Sigmund IK, Holinka J, Gamper J, Staats K, Böhler C, Kubista B, et al. Qualitative α-defensin test (synovasure) for the diagnosis of periprosthetic infection in revision total joint arthroplasty. Bone Joint J. 2017;99-B:66–72. doi:10.1302/0301-620X.99B1.BJJ-2016-0295.R1.

Authors: Montri D. Wongworawat, Jay Shah, Grigor Grigoryan, Jonathan D. Creech

QUESTION 2: Does the presence of both an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) below the periprosthetic joint infection (PJI) thresholds rule out the diagnosis of a PJI?

RECOMMENDATION: Serum ESR and CRP levels below the threshold (as determined by the MusculoSkeletal Infection Society (MSIS) and International Consensus Meeting (ICM)) does not exclude the diagnosis of a PJI. Serum levels of ESR and CRP can be normal in some cases of PJI caused by slow-growing organisms.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The diagnosis of PJI is one of the biggest challenges facing the orthopaedic community. There is no absolute test for diagnosis; hence, for a patient who is suspected to have a PJI, clinicians have to use a combination of tests. The first definition for PJI was developed by the MSIS that was later modified by the ICM on PJI in 2013. Based on this definition, the cutoff for ESR was defined as >30 mm/hr and >10mg/L and for CRP (>100 mg/L for acute PJIs) [1]. According to the diagnostic guidelines of the American Academy of Orthopaedic Surgeons (AAOS), serum ESR and CRP are the first line for screening patients who are suspected for PJI [2]. The document introducing the MSIS criteria for PJI explicitly stated that some of the diagnostic markers including ESR and CRP may be normal in the presence of PJI caused by slow-growing organisms that do not elicit physiological inflammation such as *Cutibacterium acnes (C. Acnes)* [3–5].

McArthur et al. [6] reported a 4% incidence of PJI cases that were seronegative (negative ESR and CRP). Most of the patients in this study who had PJI were infected with slow growing organisms including coagulase negative Staphylococcus, *C. acnes* and Corynebacterium. Three patients in their cohort were infected with virulent organisms; however, all had received antibiotics prior to their diagnostic workup. Nozdo et al. [7] reported that PJI cases with *C. acnes* induced a milder systemic response compared to methicillin-sensitive *Staphyloccous aureus* (MSSA) and that high clinical suspicion and prolonged cultures were essential to diagnose PJI in these patients. In another study by Figa et al. [8], authors showed that *C. acnes* PJIs had below threshold values for ESR and CRP in over half their cohort.

Combined ESR and CRP are also often falsely negative. Johnson et al. [9] reported an 11.1% false negative rate for combined ESR and CRP when the MSIS criteria were considered for diagnosis. Authors concluded that this is due to an insufficient inflammatory response mounted by certain patients with PJI, leading to the muted serological levels. Other studies were in line with this finding: Saleh et al. [10] concluded that combined ESR and CRP increased the specificity at a cost of sensitivity. Shahi et al. [11] reported the sensitivity and specificity of combined ESR and CRP to be 84 and 47%, respectively.

Administration of therapeutic antibiotics prior to diagnostic workups in PJI patients can also be a cause for falsely negative ESR and CRP. This can be an additional source of missed diagnosis of PJIs if only ESR and CRP are utilized for screening, as was shown in a study by Shahi et al. [12].

Diagnosis of acute PJI in the early postoperative period is also a challenge as these markers are usually elevated in this phase. Alijanipour et al. [13] did a retrospective study and investigated the suggested thresholds for serological markers. Authors concluded that a different threshold should be used for evaluating patients in the early postoperative period. In another study by Yi et al. [14],